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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,008	11/17/2003	Masaaki Ikeda	64517.000002	5744

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
08/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,008	IKEDA ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-8,16-33 and 37-39* is/are pending in the application.

4a) Of the above claim(s) *7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,16-33 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/9/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' amendment and submission filed on June 9, 2009 that includes a response to the Advisory action dated February 9, 2009, has been entered. Claim 1, 2, 16, 37 and 38 have been amended, claims 7 and 8 cancelled, and claim 39 newly added. Accordingly, claims 1, 2, 6-8, 16-33 and 37-39 are pending in the application. Claims 7 and 8 stand withdrawn from further consideration, with traverse, as drawn to non-elected inventions.

Claims 1, 2, 6, 16-33 and 37-39 are under current examination.

Objection to the Title

The title of the disclosure is objected as not being commensurate in scope with the claimed invention. MPEP 606 states: The title should be brief but technically accurate and descriptive. The instant claims are directed to methods for proliferating cardiomyocytes, and not any terminally differentiated cell. Appropriate correction is required.

Response Maintained and New Claim Rejections - 35 USC § 112- 1st Paragraph (Scope of Enablement)

Claims 1, 2, 6, 16-33, 37 and 38 stand rejected under 35 U.S.C. 112, first paragraph, in modified form, because the specification fails to provide an enablement for the full scope of the claimed invention. The rejection set forth on pp. 4-10 of the Office action dated October 4, 2007, pp. 4-5 of the Office action dated July 9, 2008 and the Advisory action dated February 9, 2009 is

maintained in modified form for claims 1, 2, 6, 16-33, 37 and 38, and further applied to newly added claims 39 for reasons of record and the commentary provided below.

The enabled scope previously indicated has been modified to a method of proliferating cardiomyocytes comprising directly introducing into cardiomyocytes an adenoviral expression vector encoding cyclin D1, D2 or D3 and cyclin dependent kinase CDK4 or CDK 6, wherein either at least one D-type cyclin gene or cyclin dependent kinase gene is operably linked to a nuclear localization signal, and cultivating the transfected cardiomyocytes.

The scope of enablement for the instant invention is consistent with the teachings of the instant specification and the prior art that a single operably linked nuclear localization signal is sufficient to transport a cyclin D1 and a cyclin dependent kinase as a formed complex, into the nucleus.

Applicants' claim amendments have addressed the grounds of rejection only in part. The previous Office actions indicated issues regarding the use of any type of vector for introducing the cyclin and CDK genes, as instantly claimed. Base claims 1, 2 and 37 broadly encompass using any type of vector for gene delivery, including bacterial plasmids having no eukaryotic expression control elements such as promoters. Claims 31, 32, 33 and 38 are directed to using any viral vector, that include retroviruses.

With respect to gene delivery, it was previously indicated that the instant specification exemplifies the delivery of the a cyclin D1 gene operably linked to a nuclear localization signal, and a CDK4 gene via an adenoviral expression vector, by direct administration of the vector to the apical myocardium. However, it is well known in the art that any vector (as instantly claimed), that would include naked plasmid DNA delivered systemically would not result in targeted delivery or impart sufficient gene expression. Further, such expression would be transient. Moreover, terminally differentiated, non-replicating cells, such as cardiomyocytes would be refractive to viral infection by retroviruses, that require actively dividing cells as hosts. Thus, any vector or any viral vector would not predictably provide sufficient directed delivery and expression of the cyclin and CDK genes, absent further undue experimentation.

Applicants traverse the rejection, arguing that the Office Action fails to establish a *prima facie* case of enablement; and does not provide any evidence that any vector or any viral vector would not provide sufficient directed delivery and expression of the cyclin and CDK genes.

Applicants further argue that the state of art establishes that the use of vectors (including non-adenoviral vectors) is enabled, citing various U.S. Patents. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that while an enabled scope has been indicated for adenoviral expression vectors, instant base claims 1 and 2 are directed to any type of vector, that would include a bacterial plasmid, omitting an operably linked eukaryotic promoter necessary for the expression of the nuclear localization signal, the cyclin genes and a gene coding for CDK4 or CDK6. Further, as previously indicated, each patent Application is examined on its own merits and the instant Application is separate and distinct from the Patents cited by Applicants. The instant claims encompass any vectors, including bacterial shuttle vectors, having no eukaryotic promoters. Moreover, the claimed cyclin and CDK genes and the nuclear localization signal are not operably linked to any eukaryotic promoter.

With regard to lack of evidence in support of the rejection, Applicants are directed to the post-filing art of Gojo et al. (Ann. R. Coll. Surg. Engl. 84:297-301; 2002) wherein the advantages and disadvantages of various gene therapy approaches are reviewed. Specifically, Table 1, p. 298 comparing non-viral and viral gene delivery, notes that naked plasmid results in transient expression, and that retroviruses are unable to infect non-dividing cells. As stated in MPEP 2164.05(a), If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993).

With reference to the Declaration Under 37 C.F.R. §1.132 by Uichi Koshimizu, Ph.D., Applicants argue that "numerous methods of stably and efficiently transferring cardiomyocytes with foreign DNA were well known in the art at the time the '008 application was flied. Such is not found persuasive, because in none to the references cited by Dr. Koshimizu, was a gene of interest expressed in the absence of an operably linked eukaryotic promoter. The examples did not include bacterial shuttle vectors having no eukaryotic expression control elements and the only cited art allegedly relevant to retroviral vector gene transfer (Exhibit G), fails to exemplify using a retrovirus, and is further directed to cardiac allografts, and not non-dividing cardiomyocytes.

Therefore the rejection is maintained in modified form for claims 1, 2, 6, 16-33, 37 and 38, and further applied to newly added claim 39, for reasons of record and the foregoing discussion.

Conclusion

Claims 1, 2, 6, 16-33 and 37-39 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633